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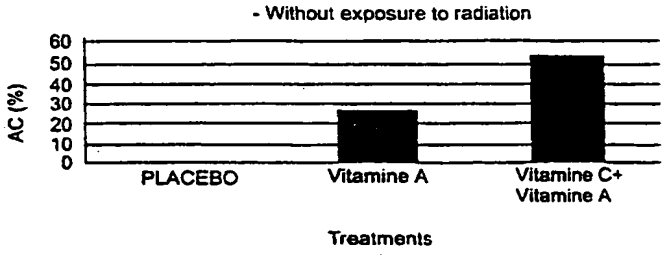
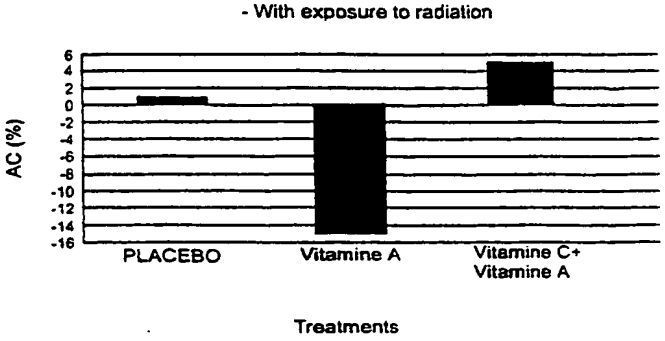
(54) Title: PROCESS AND COMPOSITION FOR ENHANCING THE ACTION OF VITAMIN A ON THE CELLULAR ACTIVITY OF AN INDIVIDUAL, AND USE OF VITAMIN C

(57) Abstract

The present invention refers to a process, a composition and the use of Vitamin C for enhancing the action of Vitamin A on the cellular activity of an individual. According to the invention, the association of Vitamin C to Vitamin A will be applied to said individual at a weight ratio ranging from 1:1 to about 10:1.





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Title: "PROCESS AND COMPOSITION FOR ENHANCING THE ACTION OF VITAMIN A ON THE CELLULAR ACTIVITY OF AN INDIVIDUAL, AND USE OF VITAMIN C"

Field of the Invention

The present invention refers to a process for improving the effects of Vitamin A used in cosmetic compositions in order to enhance the cellular activity of an individual.

Background of the Invention

The compound generically known as Vitamin A comprises retinol and its derivatives, also known as retinoids, in addition to its acidic or aldehyde form, respectively retinoic acid and retinal. Retinoic acid has application in the pharmaceutical and cosmetic industries being, however, prohibited in several countries for cosmetic use due to the adverse effects of irritability which it may cause. Examples of pharmaceutical applications of retinoic acid can be found in the article "Relationships between structure and activity of retinoids", published by Nature, Volume 236, pages 110-113, of September 9, 1996.

In the cosmetic area Vitamin A is usually employed in the form of retinol or some of its retinoids such as retinyl palmitate, and the use of retinol causes various biologic activities, many of which are highly desirable in cosmetic compositions, particularly in those intended to improve the general conditions of the skin of the individual subjected to the topic use thereof. Results achieved by the topic use of Vitamin A are described in passages contained in pages 82 - 119 of the article entitled "Vitamin A Complex", written by Wade Cheng, PhD and Shirley DePetris and published by Skin Inc., March/April 1998.

Moreover, regulation and balance of the epidermal cellular growth through the total synthesis of collagen, among others, such as retention of water in the skin, are also known as effects resulting from the use of Vitamin A in its pure form, called Retinol.

One problem resulting from the use of Vitamin A, either in its pure form or as a derivative, is that, on the one side it promotes the effects of increasing the cellular activity at the level of the dermis and epidermis, accelerating the process of proliferation and differentiation of the keratinocytes and reorganization of the fibers of the dermis (collagen and elastin). But on the other side it must be administered at low doses due to its toxicity. This fact limits the use of Vitamin A and its derivatives to lower contents or requires the utilization of other means that are able to minimize the discomfort of irritation in the skin.

In fact, the use of retinol at low contents is quite common, as shown by several studies, such as the one conducted by the Hamburg Clinic of Experimental Dermatology, in Germany, which doscloses tests with low contents of Retinol (0.034%) for men and women with age between 22 and 34 years and which show that such a concentration of retinol could reduce the amount and the deepness of wrinkles. Therefore, this study generically shows the effect of reducing wrinkles by the use of low contents of retinol.

On the other hand, what has been observed is that, even though low concentrations of retinol effectively cause little or no irritation, the results on the skin can remain below the desired levels for the present standards of demand of the consumers in view of the small amount of retinol incorporated in the cosmetic composition and available for its biological action.

In this respect, there have been attempts to obtain compositions of Vitamin A that present effective action and do not cause adverse effects, for instance, the irritation of the skin. As an example, documents US 5516793 and US 5703122 in the name of Avon Products, Inc., are incorporated herein as prior art references. These documents describe a generic association of amounts ranging from 0.5 to 25% by weight of Vitamin C with several irritating active principles, among which Vitamin A is included. This association, however, has the exclusive purpose of reducing irritation of the skin caused by Vitamin A.

It is therefore an objective of the present invention to provide an alternative for the use of Vitamin A at such concentrations that enable an increase in its properties which are beneficial to the skin, without presenting the problems cited above.

Summary of the Invention

The present invention refers to a process for enhancing the action of Vitamin A on the cellular activity of an individual comprising the association of Vitamin C with Vitamin

A, which will be applied to the referred-to individual at a weight ratio ranging from about 1:1 to about 10:1.

In another aspect, the invention refers to a composition for enhancing the action of Vitamin A on the cellular activity of an individual comprising Vitamin C in association with Vitamin A at a weight ratio in the range from about 1:1 to 10:1.

The invention further refers to the use of Vitamin C for enhancing the action of Vitamin A on the cellular activity of an individual.

Brief Description of the Drawings

- Figure 1 shows a graph representing the increase obtained in the cellular activity of a reconstituted skin by the synergistic effect of an association of Vitamin C with Vitamin A according to the invention as compared to the cellular activity of a reconstituted skin treated only with pure Vitamin A.

- Figure 2 shows the synergistic effect on the recuperation and the increase in the cellular activity in reconstituted skin treated with Vitamin A associated with Vitamin C when subjected to ultraviolet irradiation.

Detailed Description of the Invention

After detailed studies the inventors have found that the association of Vitamin C added to compositions containing Vitamin A at a weight ratio ranging from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 2:1, provides a surprising increase in the cellular activity effects of Vitamin A on an individual.

"Vitamin C" useful for the present invention comprises Vitamin C in its pure form or its derivatives, namely L-ascorbic acid in its molecular form as well as its salts and esters such as ascorbyl phosphate.

As used herein, the expression "an increase in the cellular activity" means the occurrence of a benefit brought about by the increase or improvement at least in one of the situations selected from the maintenance of the cellular condition, the cellular proliferation and the metabolic activity especially in cutaneous cells.

Tests carried out on reconstituted skin show that a treatment of the skin *in vitro* with the association of Vitamin C with Vitamin A according to the present invention promotes an unexpected synergistic increase in the cellular activity of 100% as compared to the cellular activity observed in the same skin treated exclusively with pure Vitamin A or retinol (figure 1).

In the same surprising way, it has been noted that the association of Vitamin C with Vitamin A promotes reconstitution, recuperation and increase in the cellular activity of the skin, even when the individual is subjected to ultraviolet irradiation, which is recognized to cause deleterious effects on the skin and its cells. Tests carried out to this respect show a synergistic effect of reconstitution and increase in the cellular activity of 5% on reconstituted skin treated with Vitamin A associated with Vitamin C when subjected to ultraviolet irradiation (figure 2).

The association of Vitamin C with Vitamin A according to the present invention may be carried out at the moment of the application of these compounds to the individual, but it can also be advantageously formulated as a cosmetic composition containing the two vitamins at a weight ratio ranging from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 2:1 of Vitamin C to Vitamin A.

According to a preferred embodiment of the invention, said cosmetic composition comprises, by weight, about 0.01 to about 0.9% of Vitamin C and from about 0.008 to about 0.20% of Vitamin A, based on the total weight of the composition. Even more preferably, the composition contains from about 0.02 to about 0.8% by weight of Vitamin C and from about 0.009 to about 0.16% by weight, of Vitamin A and even more preferably the composition contains 0.02 wt.% of Vitamin C and from about 0.009 to about 0.02 wt% Vitamin A, all the percentages based on the total weight of the composition.

It is noted that, even at very low concentrations, Vitamin A associated with Vitamin C as defined in the present invention achieves the desired effects of increase in the cellular activity.

The cosmetic compositions containing Vitamin A and Vitamin C at the proportions cited above can also contain other appropriate additives and formulation aids, such as antioxidants for combating free radicals. Among the useful antioxidants, Vitamin E stands out, both in its pure form presented by di-α-tocopherol, and as its derivatives such as dil-α-tocopherol, or 2,6-di-terc-buthyl-p-cresol (BHT).

In a particularly preferred way, the cosmetic compositions according to the present invention are formulated in such a manner, that their components are contained in organic vectors such as microspheres and, more particularly, in microspheres or microcapsules containing biologically active material ("Talasferas") such as those defined in US Pat 5,395,620, or in Brazilian patent application PI 9706994-7, filed in the name of this same applicant.

The composition as described above may contain a plurality of said microspheres, in a dispersed form, comprising Vitamin A and, for example, an antioxidant such as Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres. A particularly preferred composition comprises a first group of microspheres containing Vitamin A at an average concentration of 0.014% and Vitamin E at an average concentration of 0.0005% by weight, and a second group of microspheres containing 0.02% by weight of Vitamin C.

Advantageously, in association to the groups of microspheres previously mentioned, such a composition may further contain, in addition to Vitamin A and Vitamin E, cosmetic compounds selected from the group comprising skin structurers, preferably squalan and sphingolipide complexes, skin micronutrients, preferably seaweed extract, sensorial agents, for example, moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glyclol and cethyl lactate and silicones such as cyclomethicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin and soybean lecitin, thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragrances, conservants, water and mixtures thereof.

In one particular embodiment of the present invention, the composition containing Vitamin A and Vitamin C may be in the form of an emulsion and, in this case, the Vitamin C preferably used is L-ascorbic acid stabilized by hydrogen-bridge-forming compounds. Such processes of stabilizing L-ascorbic acid are described in applications PI 9704418-0 and PI 9704728-7, also filed by this same applicant.

As an illustrative example of another possible embodiment of the present invention, the composition is formulated as a gel in which the weight ratio of Vitamin C to Vitamin A is advantageously about 5:1, Vitamin C being present preferably in amounts of about 0.75% and Vitamin C being present in amounts of about 0.16 wt.%, based on the total

weight of the composition. This gel composition may further contain thickeners such as carbopol, fragrances, conservants and water.

Claims

1. A process for enhancing the action of Vitamin A on the cellular activity of an individual, characterized by comprising the association of Vitamin C to Vitamin A, which will be applied to said individual at a weight ratio ranging from about 1:1 to about 10:1 of Vitamin C to Vitamin A.

2. A process according to claim 1, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 5:1.

3. A process according to claim 2, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 2:1.

4. A process according to any one of claims 1 - 3, characterized in that Vitamin C is L-ascorbic acid stabilized with hydrogen-bridge-forming compounds.

5. A composition for enhancing the action of Vitamin A on the cellular activity of an individual, characterized by comprising Vitamin C in association with Vitamin A at a weight ratio ranging from about 1:1 to about 10:1 of Vitamin C to Vitamin A.

6. A composition according to claim 5, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 5:1.

7. A composition according to claim 6, characterized in that the weight ratio of Vitamin C to Vitamin A is of about 5:1, Vitamin C being present at a concentration of about 0.75% and Vitamin A being present at contents of about 0.16%, and in that it optionally contains thickeners, preferably carbopol, fragrances, conservants and water.

8. A composition according to claim 6, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 2:1.

9. A composition according to claim 5, characterized in that Vitamin C is present at a concentration of about 0.01% to 0.99% by weight, and Vitamin A is present at a concentration of about 0.008% to 0.20% by weight, based on the total weight of the composition.

10. A composition according to claim 8, characterized in that Vitamin C is present at a concentration of about 0.02% to 0.8% by weight, and Vitamin A is present at a concentration of about 0.009% to 0.16% by weight, based on the total weight of the composition.

11. A composition according to claim 5, characterized ion that Vitamin C is present at a composition of about 0.02% by weight, and Vitamin A is present at a concentration of about 0.009% to 0.02% by weight, based on the total weight of the composition.

12. A composition according to claim 11, characterized ion that it contains a plurality of dispersed microspheres, said plurality of microspheres comprising Vitamin A and an antioxidant, preferably Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres.

13. A composition according to claim 12, characterized in that Vitamin C is contained in the second group of microspheres at a concentration of 0.02%.

14. A composition according to claim 13, characterized ion that it contains a first group of microspheres containing Vitamin A at an average concentration of 0.014% and Vitamin E at an average concentration of 0.0005%, by weight, and cosmetic compounds selected from the group consisting of skin structurers, preferably squalan and sphingolipide complexes, micronutrients of the skin, preferably seaweed extract, sensorial agents, preferably moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glyclol and cethyl lactate and silicones such as cyclomethicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin and soybean lecitin, thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragances, conservants, water and mixtures thereof.

15. A composition according to any one of claims 5 - 14, characterized in that Vitamin C is L-ascorbic acid stabilized with hydrogen-bridge-forming compounds.

16. Use of Vitamin C, characterized in that it is for enhancing the action of Vitamin A on the cellular activity of an individual.

FIG. 1 - Without exposure to radiation

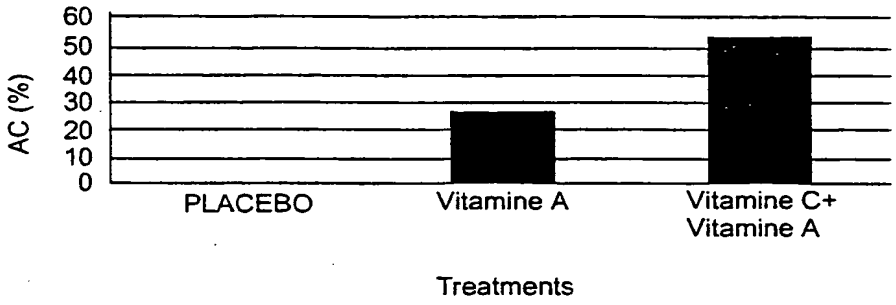
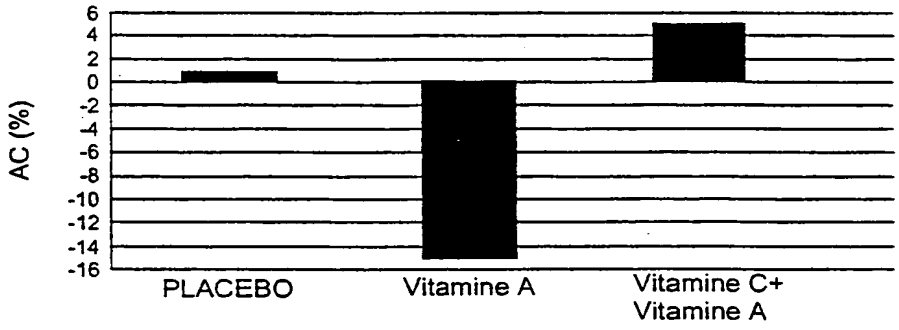


FIG. 2 - With exposure to radiation



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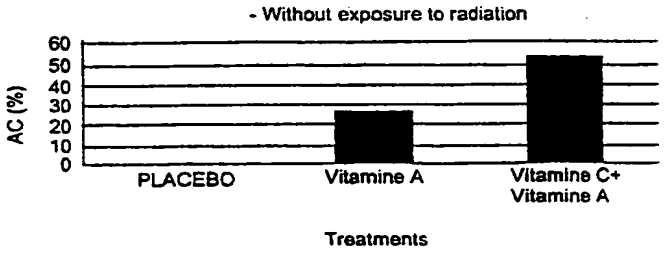

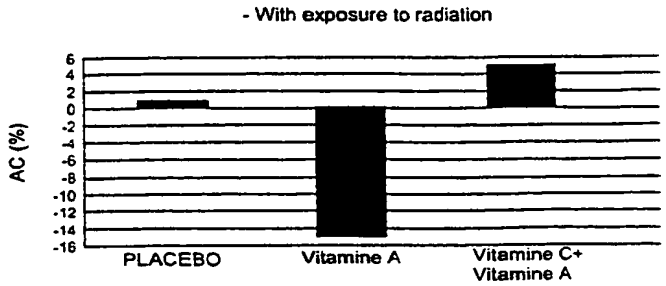

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5 891 470 A (RINALDI MARIE A ET AL) 6 April 1999 (1999-04-06) column 7, line 45 -column 8, line 28 column 9, line 10 - line 30 column 10, line 16 -column 11, line 19; claims ---	1-16
P,X	WO 99 33439 A (ROBERTS RICHARD L ;GREENE JAMES A (US); SHAKLEE CORP (US); SIDDIQU) 8 July 1999 (1999-07-08) page 6, line 3 - line 14; claims 1-10,1624 ---	1-16
P,X	WO 99 24011 A (MURAD HOWARD) 20 May 1999 (1999-05-20) page 9, line 3 - line 15 page 10, line 17 - line 28; claims --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2000	25.04.00

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte tional Application No
PCT/BR 99/00072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 781 551 A (ADVANCED POLYMER SYSTEMS INC) 2 July 1997 (1997-07-02) page 2, line 43 -page 3, line 24 page 5, line 1 -page 6, line 21; claims ---	1-16
X	EP 0 229 561 A (MOET HENNESSY RECH) 22 July 1987 (1987-07-22) page 2, line 43 - line 46 page 3, line 38 - line 43 page 11, line 18 - line 31 page 13, line 1 - line 26; claims 1-3,11-14 ---	1-16
X	DATABASE STN INTERNATIONAL "Waging war on wrinkles" retrieved from FILE PROMT, accession no. 1998:413143 XP002900870 abstract & EUROPEAN COSMETIC MARKETS, August 1998 (1998-08), ISSN: 0957-1515 ---	1-16
X	WO 94 09756 A (UNILEVER PLC ;UNILEVER NV (NL)) 11 May 1994 (1994-05-11) page 4, line 24 - line 35 page 23, line 1 - line 25; claims ---	1-16
X	FR 2 612 775 A (THOREL JEAN) 30 September 1988 (1988-09-30) page 3, line 19 - line 23; claims 1-3 ---	1-16
X	US 4 704 280 A (BATES HARRY L) 3 November 1987 (1987-11-03) the whole document ---	1-16
X	DATABASE WPI Section Ch, Week 198706 Derwent Publications Ltd., London, GB; Class B03, AN 1987-040730 XP002900871 & JP 62 000013 A (MIHAMA H), 6 January 1987 (1987-01-06) abstract ---	5-11
X	WO 93 00015 A (KALAMAZOO HOLDINGS INC) 7 January 1993 (1993-01-07) claims 8,9 -----	5-11

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 99/ 00072

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-4, 16 all in part
because they relate to subject matter not required to be searched by this Authority, namely:
See next sheet

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 99/00072

Claims 1-4, 16 all in part relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds compositions.

INTERNATIONAL SEARCH REPORT

ma[redacted] patent family members

Internat[redacted]ication No
PCT/GB[redacted]/00072

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